

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 September 2002 (19.09.2002)

PCT

(10) International Publication Number
WO 02/072093 A2

(51) International Patent Classification⁷: **A61K 31/445**,
A61P 25/28

(21) International Application Number: PCT/US02/03975

(22) International Filing Date: 6 February 2002 (06.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/267,352 8 February 2001 (08.02.2001) US

(71) Applicant: **SCHERING CORPORATION** [US/US];
2000 Galloping Hill Road, Kenilworth, NJ 07033-0530
(US).

(72) Inventors: **HEY, John, A.**; 23 Willow Avenue, Randolph,
NJ 07869 (US). **ASLANIAN, Robert, G.**; 144 Philip
Drive, Rockaway, NJ 07866 (US).

(74) Agent: **MAGATTI, Anita, W.**; Schering Corporation,
Patent Department, K-6-1 1990, 2000 Galloping Hill
Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ,
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU,
ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV,
MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT,
RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
UZ, VN, YU, ZA, ZM.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Declaration under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations*

Published:

— *without international search report and to be republished
upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

WO 02/072093 A2

(54) Title: USE OF DUAL H₃/M₂ ANTAGONISTS IN THE TREATMENT OF COGNITION DEFICIT DISORDERS

(57) Abstract: This invention relates to the use of a dual histamine H₃ receptor antagonist / m₂ muscarinic antagonist, or a combination of a histamine H₃ receptor antagonist and a m₂ muscarinic antagonist, optionally in further combination with an acetylcholinesterase inhibitor, for the preparation of a medicament for the treatment of cognition deficit disorders.

USE OF DUAL H₃/M₂ ANTAGONISTS
IN THE TREATMENT OF COGNITION DEFICIT DISORDERS

BACKGROUND

This invention relates to the treatment of cognition deficit disorders by administering a dual histamine H₃ receptor antagonist / m₂ muscarinic antagonist, or a combination of an histamine H₃ receptor antagonist and a m₂ muscarinic antagonist. In particular, the invention relates to the treatment of cognition deficit diseases such as Alzheimer's Disease (AD) or other CNS learning disorders such as attention deficit disorder and autism.

European Patent Application No. 0 420 396 A2 and Howson *et al.*, *Bioorg. & Med. Chem. Letters*, Vol. 2 No. 1 (1992), pp. 77-78, describe imidazole derivatives having an amidine group as H₃ agonists. Van der Groot *et al.* (*Eur. J. Med. Chem.* (1992) Vol. 27, pp. 511-517) describe isothioureia analogs of histamine as potent agonists or antagonists of the histamine H₃ receptor, and these isothioureia analogs of histamine overlap in part with those of the two references cited above. Clapham *et al.*, *J. Psychopharmacol.* (British Assn. for Psychopharmacology, July 25-28 1993, Abstr. Book), A17] describes the ability of histamine H₃ receptor antagonists to improve cognition and to increase release of acetylcholine *in vivo* in the rat. Clapham *et al.*, *Brit. J. Pharm. Suppl.*, 1993, 110, Abstract 65P, presents results showing that thioperamide can improve short-term memory and reversal learning in the rat and implicate the involvement of H₃ receptors in the modulation of cognitive function. Yokoyama *et al.*, *Eur. J. Pharmacol.*, vol. 234 (1993), pp. 129-133, reports how thioperamide decreased the duration of each phase of convulsion and raised the electroconvulsive threshold, and go on to suggest that these and other findings support the hypothesis that the central histaminergic system is involved in the inhibition of seizures. WO 9301812-A1 describes the use of S-[3-(4(5)-imidazolyl)propyl]-isothioureia as a histamine H₃ antagonist, especially for treating cognitive disorders, e.g. Alzheimer's disease and age-related memory impairment.

- 2 -

Schlicker et al. describe a number of imidazolylalkyl compounds wherein the imidazolylalkyl group is bonded to a guanidine group, an ester group or an amide group (including thioamide and urea), and compare these to thioperamide. Leurs et al., *Progr. Drug Res.* (1992) vol. 39, pp. 127-165, and Lipp et al. *The Histamine*
5 *Receptor*, eds.: Schwartz and Haas, Wiley-Liss, New York (1992), pp. 57-72, review a variety of synthetic H₃ receptor antagonists, and Lipp et al. (*ibid.*) have defined the necessary structural requirements for an H₃ receptor antagonist.

Several muscarinic receptor subtypes have been identified, i.e., m₁, m₂, m₃, m₄ and m₅, and the potential therapeutic effects of the various subtypes have been the
10 subject of many publications. See, for example, US 5,446,057, wherein the m₁ receptor was identified as mediating gastric secretion; m₂ and m₃ receptors were identified as mediating nasal mucosal secretions; and m₂ was identified as mediating cardiovascular conditions and CNS conditions associated with release of acetylcholine, e.g., Alzheimer's disease and other dementias. Muscarinic receptors in
15 general were reported to be mediators of cholinergic neurotransmission.

SUMMARY OF THE INVENTION

This invention relates to the use of a dual histamine H₃ receptor antagonist / m₂ muscarinic antagonist, or a combination of an histamine H₃ receptor antagonist and a
20 m₂ muscarinic antagonist for the preparation of a medicament for the treatment of cognition deficit disorders. In particular, the invention relates to use of the dual antagonists or the combination of antagonists in the treatment of Alzheimer's Disease, attention deficit disorder or autism.

The dual H₃ / m₂ antagonist compounds of the invention are preferably
25 administered as a pharmaceutical composition comprising the dual antagonist and a pharmaceutically acceptable carrier. When separate H₃ and m₂ antagonists are used in combination, an effective amount of the combination of a H₃ antagonist and a m₂ antagonist can be combined with a pharmaceutically acceptable carrier in a single pharmaceutical composition. Alternatively, a pharmaceutical composition comprising
30 a H₃ antagonist and a separate pharmaceutical composition comprising a m₂ antagonist can be administered, simultaneously or sequentially, wherein the individual antagonists are administered in amounts chosen so that the combination is effective to treat cognition deficit disorders. Kits comprising separate H₃ and m₂ pharmaceutical compositions in a single package are also contemplated.

35 In still another aspect, the invention relates to the use of a dual histamine H₃ receptor antagonist / m₂ muscarinic antagonist, or a combination of an histamine H₃ receptor antagonist and a m₂ muscarinic antagonist, in further combination with an acetylcholinesterase inhibitor, for the preparation of a medicament for the treatment of

- 3 -

a cognition deficit disorder or a neurodegenerative disease. Pharmaceutical compositions comprising a dual histamine H_3 receptor antagonist / m_2 muscarinic antagonist and an acetylcholinesterase inhibitor in a pharmaceutically acceptable carrier, or separate H_3 and m_2 antagonists and an acetylcholinesterase inhibitor in a pharmaceutically acceptable carrier are contemplated. Kits comprising separate dual H_3/m_2 antagonist and acetylcholinesterase inhibitor pharmaceutical compositions, and separate H_3 , m_2 and acetylcholinesterase inhibitor pharmaceutical compositions in a single package are also contemplated.

This invention also relates to a method of treating cognition deficit disorders comprising administering to a mammal in need of such treatment an effective amount of a dual histamine H_3 receptor antagonist / m_2 muscarinic antagonist, or a combination of an histamine H_3 receptor antagonist and a m_2 muscarinic antagonist.

In still another aspect, the invention relates to a method for treating a cognitive disease or neurodegenerative disease comprising administering to a mammal in need of such treatment an effective amount of a dual histamine H_3 receptor antagonist / m_2 muscarinic antagonist, or a combination of an histamine H_3 receptor antagonist and a m_2 muscarinic antagonist, in further combination with an acetylcholinesterase inhibitor.

20 DETAILED DESCRIPTION

Dual H_3/m_2 antagonists of the present invention are exemplified by the compounds shown in the following table:

Compound Number	Structure
1	
2	
3	
4	
5	

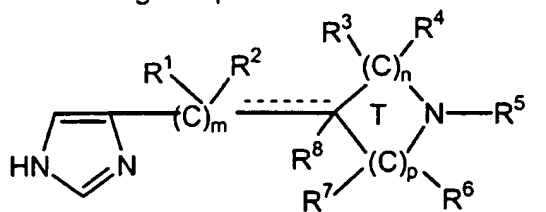
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	

Other compounds having dual H₃/m₂ antagonist activity can be identified by evaluating the compounds for activity at H₃ receptors and activity at m₂ receptors using the test methods described below.

- 5 -

The currently known histamine H₃ receptor antagonists cannot be easily classified chemically, but include, without limitation: thioperamide, impromidine, burimamide, clobenpropit, impentamine, mifetidine, clozapine, S-sopromidine, R-sopromidine, ciproxifam, SKF-91486, GR-175737, GT-2016, GT-2331 and UCL-1199.

Certain H₃ antagonists are disclosed in several US patents. US 5,463,074 discloses the following compounds:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

- 10 (A) m is an integer selected from the group consisting of: 0, 1, and 2;
- (B) n and p are integers and are each independently selected from the group consisting of: 0, 1, 2, and 3 such that the sum of n and p is 2 or 3;
- (C) each R¹, R², R³, R⁴, R⁶, R⁷, and R⁸ is independently selected from the group consisting of:
 - 15 (1) H;
 - (2) C₁ to C₆ alkyl;
 - (3) C₃ to C₆ cycloalkyl; and
 - (4) -(CH₂)_q-R⁹ wherein q is an integer of: 1 to 7, and R⁹ is selected from the group consisting of: phenyl, substituted phenyl, -OR¹⁰, -C(O)OR¹⁰, -C(O)R¹⁰, -OC(O)R¹⁰, -C(O)NR¹⁰R¹¹, CN and -SR¹⁰ wherein R¹⁰ and R¹¹ are as defined
 - 20 below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C₁ to C₆)alkyl, halogen, C₁ to C₆ alkyl, -CF₃, -CN, and -NO₂, and wherein said substituted phenyl contains from 1 to 3 substituents;
- 25 (D) R⁵ is selected from the group consisting of:
 - (1) H;
 - (2) C₁ to C₂₀ alkyl;
 - (3) C₃ to C₆ cycloalkyl;
 - (4) -C(O)OR^{10'}; wherein R^{10'} is the same as R¹⁰ defined below except that
 - 30 R^{10'} is not H;
 - (5) -C(O)R¹⁰;
 - (6) -C(O)NR¹⁰R¹¹;
 - (7) allyl;
 - (8) propargyl; and

- 6 -

(9) $-(CH_2)_q-R^9$, wherein q and R^9 are as defined above with the proviso that when q is 1 then R^9 is not $-OH$ or $-SH$;

(E) R^{10} and R^{11} are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, and C_3 to C_6 cycloalkyl; and, for the substituent $-C(O)NR^{10}R^{11}$, R^{10} and R^{11} , together with the nitrogen to which they are bound, can form a ring having 5, 6, or 7 atoms;

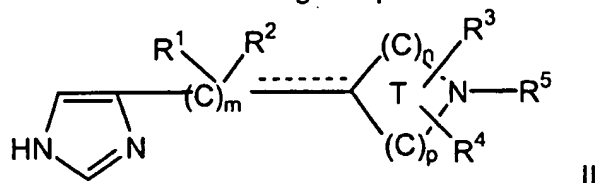
(F) the dotted line (-----) represents a double bond that is optionally present when m is 1, and T is a 5-membered ring, and n is not 0, and p is not 0, and when said double bond is present then R^2 and R^8 are absent;

(G) when m is 2, each R^1 is the same or different substituent for each m , and each R^2 is the same or different substituent for each m ;

(H) when n is 2 or 3, each R^3 is the same or different substituent for each n , and each R^4 is the same or different substituent for each n ; and

(I) when p is 2 or 3, each R^6 is the same or different substituent for each p , and each R^7 is the same or different substituent for each p .

US 5,807,872 discloses the following compounds:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) m is 1 or 2;

(B) n and p are independently selected from 0, 1, 2, 3, and 4 such that the sum of n and p is 4 and T is a 6-membered ring;

(C) R^3 and R^4 are each independently bound to the same or different carbon atom of ring T such that there is only one R^3 group and one R^4 group in ring T , and each R^1 , R^2 , R^3 , and R^4 is independently selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl; and

(3) $-(CH_2)_q-R^6$ wherein q is an integer of: 1 to 7, and R^6 is selected from the group consisting of: phenyl, substituted phenyl, $-OR^7$, $-C(O)OR^7$, $-C(O)R^7$, $-OC(O)R^7$, $-C(O)NR^7R^8$, CN and $-SR^7$ wherein R^7 and R^8 are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: $-OH$, $-O-(C_1$ to $C_6)$ alkyl, halogen, C_1 to C_6 alkyl, $-CF_3$, $-CN$, and $-NO_2$, and wherein said substituted phenyl contains 1 to 3 substituents;

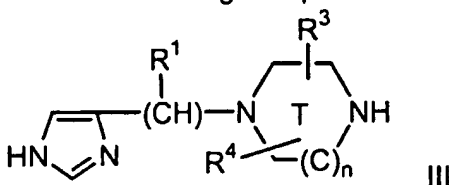
(D) R^5 is selected from the group consisting of:

- 7 -

- (1) H;
 (2) C₁ to C₂₀ alkyl;
 (3) C₃ to C₆ cycloalkyl;
 (4) -C(O)OR^{7'}; wherein R^{7'} is the same as R⁷ defined below except that R^{7'}
 5 is not H;
 (5) -C(O)R⁷;
 (6) -C(O)NR⁷R⁸;
 (7) allyl;
 (8) propargyl; and
 10 (9) -(CH₂)_q-R⁶, wherein q and R⁶ are as defined above, and when q is
 equal to 1, then R⁶ is not OH or SH;
 (E) R⁷ and R⁸ are each independently selected from the group consisting
 of: H, C₁ to C₆ alkyl, and C₃ to C₆ cycloalkyl;
 (F) the dotted line (-----) represents a double bond that is optionally present
 15 when m is 1, and n is not 0, and p is not 0, and when said double bond is present
 then R² is absent; and
 (G) when m is 2, each R¹ is the same or different substituent for each m,
 and each R² is the same or different substituent for each m, and at least two of the
 substituents R¹ and/or R² are H.

20

US 5,633,250 discloses the following compounds:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

- (A) n is 1 or 2;
 25 (B) R¹ is selected from the group consisting of:
 (1) H;
 (2) C₁ to C₆ alkyl;
 (3) allyl; and
 (4) propargyl;
 30 (C) R³ and R⁴ are independently selected from the group consisting of:
 (1) H;
 (2) C₁ to C₆ alkyl;
 (3) allyl;
 (4) propargyl; and

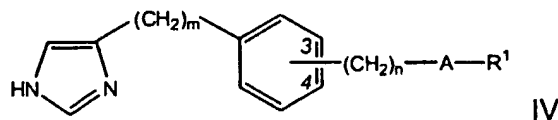
- 8 -

(5) $-(CH_2)_q-R^5$ wherein q is an integer of: 1 to 7, and R^5 is selected from the group consisting of: phenyl, substituted phenyl, $-OR^6$, $-C(O)OR^6$, $-C(O)R^6$, $-OC(O)R^6$, $-C(O)NR^6R^7$, CN and $-SR^6$ wherein R^6 and R^7 are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: $-OH$, $-O-(C_1 \text{ to } C_6)\text{alkyl}$, halogen, $C_1 \text{ to } C_6$ alkyl, $-CF_3$, $-CN$, and $-NO_2$, and wherein said substituted phenyl contains 1 to 3 substituents;

(D) R^6 and R^7 are each independently selected from the group consisting of: H and $C_1 \text{ to } C_6$ alkyl; and

(E) R^3 and R^4 are each independently bound to the same or different carbon atom of ring T.

US 5,578,616 discloses the following compounds:



wherein:

A is selected from $-O-CO-NR^1-$, $-O-CO-$, $-NR^1-CO-NR^1-$, $-NR^1-CO-$, $-NR^1-$, $-O-$, $-CO-NR^1-$, $-CO-O-$, and $-C(:NR^1)-NR^1-$;

the groups R^1 , which may be the same or different when there are 2 or 3 such groups in the molecule shown above, are selected from H, and lower alkyl, aryl, cycloalkyl, heterocyclic and heterocyclyl-alkyl groups, and groups of the formula $-(CH_2)_y-G$, where G is selected from CO_2R^3 , COR^3 , $CONR^3R^4$, OR^3 , SR^3 , NR^3R^4 , heteroaryl and phenyl, which phenyl is optionally substituted by halogen, lower alkoxy or polyhaloloweralkyl, and y is an integer from 1 to 3;

R^2 is selected from H and halogen atoms, and alkyl, alkenyl, alkynyl and trifluoromethyl groups, and groups of the formula OR^3 , SR^3 and NR^3R^4 ;

R^3 and R^4 are independently selected from H, and lower alkyl and cycloalkyl groups, or R^3 and R^4 together with the intervening nitrogen atom can form a saturated ring containing 4 to 6 carbon atoms that can be substituted with 1 or 2 lower alkyl groups;

with the proviso that, when y is 1 and G is OR^3 , SR^3 or NR^3R^4 , then neither R^3 nor R^4 is H;

the group $-(CH_2)_n-A-R^1$ is at the 3- or 4-position, and the group R^2 is at any free position;

m is an integer from 1 to 3; and

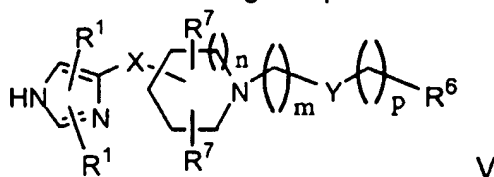
n is 0 or an integer from 1 to 3;

or a pharmaceutically acceptable acid addition salt thereof;

- 9 -

or a pharmaceutically acceptable salt thereof with a base when G is CO₂H;
including a tautomeric form thereof.

US 6,100,279 discloses the following compounds:



or pharmaceutically acceptable salts or solvates thereof, wherein:

X is a straight chain alkyl group having 1 to 7 carbon atoms or an alkene or alkyne group with 2 to 4 carbon atoms; wherein said alkyl or alkene groups are optionally substituted with up to two R⁷ groups;

n is 0, 1 or 2 ,

m and p are 0 to 4 ;

when m is 0 to 4, Y represents -SO₂-; -CS-; -CO-; -CONR⁵-; -CO(CH₂)_wO- (with w being 1 to 4); -COO-; -CON(OR⁵)-; -C(NR⁵)NR⁵-; -SO₂NR⁵- or -CSNR⁵-;

when m is 2 to 4, Y represents all the groups above when m is 0 to 4 and, in addition, Y represents -CHOR⁵-; -O-; -NR⁵CONR⁵-; -NR⁵CO-; -NR⁵-; -OCONR⁵-; -NR⁵C(NR⁵)NR⁵-; -NR⁵CSNR⁵-; -NR⁵CS- or -NR⁵SO₂-; -NR⁵C(O)O-; or -CSNR⁵-;

each R⁵ independently represents H, alkyl or benzyl;

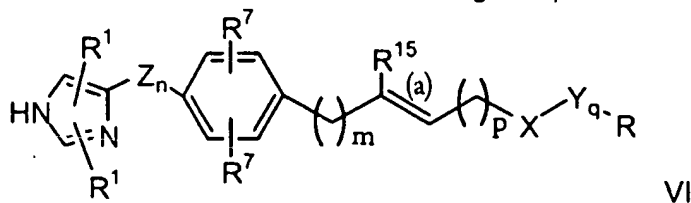
R⁶ represents aryl, heteroaryl, or a 3- to 7- membered heterocyclic group having one to three heteroatoms in the ring, wherein the heteroatoms are selected from N, S and O, and wherein said R⁶ group is optionally substituted by one to three substituents as defined below;

when Y is -SO₂ -, then R⁶, in addition to the above groups, also represents alkyl having 1 to 7 carbon atoms or a group -NR¹⁰R¹¹ wherein R¹⁰ and R¹¹ are independently selected from H, alkyl or trihalomethyl;

each R¹ is independently H, alkyl or trihalomethyl;

each R⁷ is independently selected from H, alkyl, trihalomethyl, phenyl or benzyl, wherein said phenyl and benzyl are optionally substituted by one to three substituents independently selected from alkyl, halogen, trihalomethyl, CN, NO₂, OR¹⁰ or NR¹⁰R¹¹, wherein R¹⁰ and R¹¹ are as above defined.

US 6,034,251 discloses the following compounds:



- 10 -

or a pharmaceutically acceptable salt or solvate thereof, wherein:

the double bond (a) is E or Z;

each R¹ is independently selected from the group consisting of H, lower alkyl, trihalomethyl, phenyl and benzyl;

5 each R⁷ is independently selected from the group consisting of H, lower alkyl, halogen, trihalomethyl, NR¹⁰R¹¹, or a group OR¹⁰, whereby R¹⁰ and R¹¹ are independently selected from H, lower alkyl or trihalomethyl;

X is -CONR⁵-, -SO₂-, -S-, -CO-, -COO-, -CN(OR⁵)NR⁵-, -C(NR⁵)NR⁵-, -SONR⁵-, -SO₂NR⁵- and, provided p is not zero, X may also be -O-, -NR⁵-;

10 -NR⁵CONR⁵-, -OCONR⁵-, -O-CO- or -NR⁵CO-;

Y is C₁-C₃-alkyl, optionally substituted at any carbon atom of the group by one substituent R⁵;

Z is C(R¹)₂; wherein no more than two R¹ groups are other than H;

n is 1 or 2;

15 m is 0 or 1;

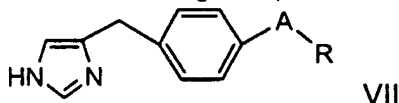
p is 0 or 1;

q is 0 or 1;

R is selected from C₃ to C₇ cycloalkyl, heterocyclic groups, aryl or heteroaryl, wherein said R groups are optionally substituted with 1-3 substituents;

20 each R⁵ independently represents H, lower alkyl or poly-haloloweralkyl; and R¹⁵ represents H or lower alkyl (e.g., methyl).

US 5,990,147 discloses the following compounds:

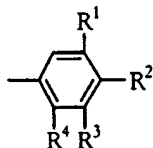


25 or a pharmaceutically acceptable acid addition salt or solvate thereof (or tautomer thereof), wherein:

A is -CH₂-NH-CO-NH-, -CH₂-O-CO-NH- or -CH₂CH₂-CO-NH-(CH₂)_m-;

m is 0, 1 or 2;

R is the group

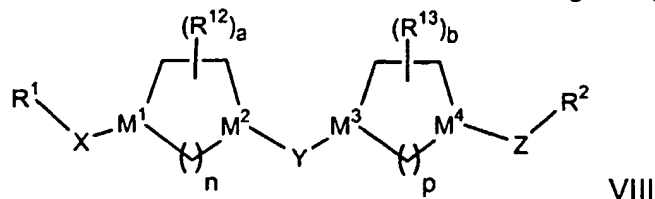


30

wherein at least two of R¹, R², R³ and R⁴ are H and the two others are independently selected from H, halogen, CH₃, CF₃, OCH₃, OCF₃ or CN; and with the proviso, that when A is -CH₂-O-CO-NH- and R¹, R³ and R⁴ are all H, then R² can not be Cl.

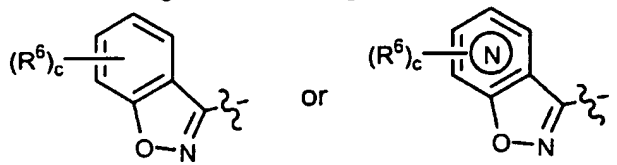
- 11 -

U.S. Application No. 09/978,267 discloses the following compounds:

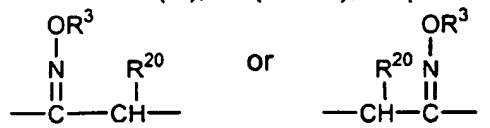


or a pharmaceutically acceptable salt or solvate thereof, wherein:

- (1) R^1 is selected from aryl, heteroaryl, heterocycloalkyl, alkyl, cycloalkyl, or alkylaryl; wherein said R^1 groups are optionally substituted with 1 to 4 substituents independently selected from: halogen, hydroxyl, lower alkoxy, $-CF_3$, CF_3O- , $-NR^4R^5$, phenyl, NO_2 , $-CO_2R^4$, $-CON(R^4)_2$ wherein each R^4 is the same or different, $-S(O)_mN(R^{20})_2$ wherein each R^{20} is the same or different H or alkyl group, or $-CN$; or
- (2) R^1 and X taken together form a group selected from:



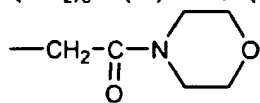
- (3) X is selected from: $=C(O)$, $=C(NOR^3)$, $=C(NNR^4R^5)$,



- (4) M^1 and M^2 are independently selected from C or N;
- (5) M^3 and M^4 are independently selected from C or N;
- (6) Y is selected from: is $-CH_2-$, $=C(O)$, $=C(NOR^{20})$, or $=C(S)$;
- (7) Z is a $C_1 - C_6$ alkyl group;
- (8) R^2 is a five or six-membered heteroaryl ring, said heteroaryl rings being

optionally substituted with 1 to 3 substituents independently selected from: halogen, hydroxyl, lower alkyl, lower alkoxy, $-CF_3$, CF_3O- , $-NR^4R^5$, phenyl, $-NO_2$, $-CO_2R^4$, $-CON(R^4)_2$ wherein each R^4 is the same or different, $-CH_2NR^4R^5$, $-(N)C(NR^4R^5)_2$, or $-CN$;

- (9) R^3 is selected from H, $C_1 - C_6$ alkyl, aryl, heteroaryl, heterocycloalkyl, arylalkyl, $-(CH_2)_6-C(O)N(R^4)_2$ wherein each R^4 is the same or different, $-(CH_2)_6-C(O)OR^4$, $-(CH_2)_6-C(O)R^{30}$ wherein R^{30} is a heterocycloalkyl group, including



, $-CF_3$, or $-CH_2CF_3$;

wherein said aryl, heteroaryl, heterocycloalkyl, and the aryl portion of said arylalkyl are optionally substituted with 1 to 3 substituents selected from: halogen, $-OH$, $-OCF_3$, $-CF_3$, $-CN$, $-N(R^{45})_2$, $-CO_2R^{45}$, or $-C(O)N(R^{45})_2$, wherein each R^{45} is independently

- 12 -

selected from: H, alkyl, alkylaryl, or alkylaryl wherein said aryl moiety is substituted with 1 to 3 substituents independently selected from $-\text{CF}_3$, $-\text{OH}$, halogen, alkyl, $-\text{NO}_2$, or $-\text{CN}$;

- (10) R^4 is selected from: H, $\text{C}_1 - \text{C}_6$ alkyl, aryl, alkylaryl, said aryl and alkylaryl groups being optionally substituted with 1 to 3 substituents selected from: halogen, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OH}$, $-\text{N}(\text{R}^{45})_2$, $-\text{CO}_2\text{R}^{45}$, $-\text{C}(\text{O})\text{N}(\text{R}^{45})_2$, or $-\text{CN}$; wherein R^{45} is as defined above;

(11) R^5 is selected from: H, $\text{C}_1 - \text{C}_6$ alkyl, $-\text{C}(\text{O})\text{R}^4$, $-\text{C}(\text{O})_2\text{R}^4$, or $-\text{C}(\text{O})\text{N}(\text{R}^4)_2$ wherein each R^4 is independently selected, and R^4 is as defined above;

- (12) or R^4 and R^5 taken together with the nitrogen atom to which they are bound forms a five or six membered heterocycloalkyl ring;

(13) R^6 is selected from: alkyl, aryl, alkylaryl, halogen, hydroxyl, lower alkoxy, $-\text{CF}_3$, $\text{CF}_3\text{O}-$, $-\text{NR}^4\text{R}^5$, phenyl, $-\text{NO}_2$, $-\text{CO}_2\text{R}^4$, $-\text{CON}(\text{R}^4)_2$ wherein each R^4 is the same or different, or $-\text{CN}$;

- (14) R^{12} is selected from: alkyl, hydroxyl, alkoxy, or fluoro;

(15) R^{13} is selected from: alkyl, hydroxyl, alkoxy, or fluoro;

(16) a is 0 to 2;

(17) b is 0 to 2;

(18) c is 0 to 2;

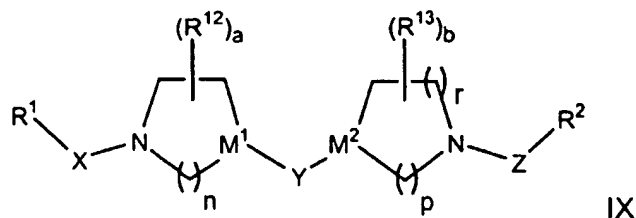
- (19) e is 0 to 5;

(20) m is 1 or 2;

(21) n is 1, 2 or 3, with the proviso that when M^1 and M^2 are both nitrogen, then n is 2 or 3; and

- (22) p is 1, 2 or 3, with the proviso that when M^3 and M^4 are both nitrogen, then p is 2 or 3.

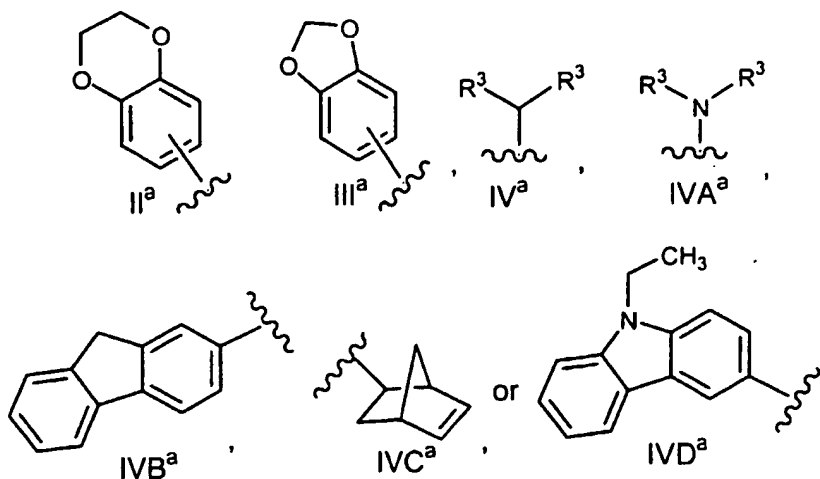
U.S. Provisional Application No. 60/275,417 discloses the following compounds:



- or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) R^1 is selected from aryl, heteroaryl, heterocycloalkyl, alkyl, $-\text{C}(\text{O})\text{N}(\text{R}^{4B})_2$, cycloalkyl, arylalkyl, heteroarylheteroaryl or a group selected from:

- 13 -



said aryl, heteroaryl, aryl portion of arylalkyl, phenyl ring of formula II^a, phenyl ring of formula III^a, phenyl rings of formula IVB^a, or phenyl rings of formula IVD^a are optionally substituted with 1 to 3 substituents independently selected from halogen; hydroxyl; lower alkoxy; -Oaryl; -SR²²; -CF₃; -OCF₃; -OCHF₂; -NR⁴R⁵; phenyl; NO₂; -CO₂R⁴; -CON(R⁴)₂, wherein each R⁴ is the same or different; -S(O)₂R²²; -S(O)₂N(R²⁰)₂, wherein each R²⁰ is the same or different; -N(R²⁴)S(O)₂R²²; -CN; -CH₂OH; -OCH₂CH₂OR²²; alkyl; substituted phenyl wherein said phenyl has 1 to 3 substituents independently selected from alkyl, halogen, -CN, -NO₂, -OCHF₂, -Oalkyl; -Oalkylaryl wherein said aryl group is optionally substituted with 1 to 3 independently selected halogens; or phenyl;

(B) X is selected from alkyl or -S(O)₂-;

(C) Y represents a single bond; or Y is selected from -C(O)-, -C(S)-, -CH₂-, or -NR⁴C(O)-; with the provisos that when M¹ is N, then Y is not -NR⁴C(O)-; and when Y is a bond, then M¹ and M² are both carbon;

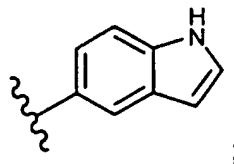
(D) M¹ and M² are independently selected from C or N;

(E) Z is selected from: C₁-C₆ alkyl, -SO₂-, -C(O)- or -C(O)NR⁴-;

(F) R² is selected from: a six-membered heteroaryl ring having 1 or 2 heteroatoms independently selected from N or N-O, with the remaining ring atoms being carbon; a five-membered heteroaryl ring having 1 to 3 heteroatoms selected from nitrogen, oxygen, or sulfur with the remaining ring atoms being carbon; an alkyl group; an aryl group wherein said substituted phenyl is substituted with 1 to 3 substituents independently selected from halogen, -Oalkyl, -OCF₃, -CF₃, -CN, -NO₂,

- 14 -

-NHC(O)CH₃, or -O(CH₂)_qN(R^{10A})₂; -N(R^{11A})₂ wherein each R^{11A} is independently selected from H, alkyl or aryl; a group of the formula



or a heteroarylheteroaryl group;

- 5 said five membered heteroaryl ring or six-membered heteroaryl ring is optionally substituted with 1 to 3 substituents selected from halogen; hydroxyl; lower alkyl; lower alkoxy; -CF₃; -NR⁴R⁵; phenyl; -NO₂; -C(O)N(R⁴)₂ (wherein each R⁴ is the same or different); -C(O)₂R⁴; or phenyl substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, -OCF₃, -CF₃, -CN, -NO₂ or
- 10 -O(CH₂)_qN(R^{10A})₂;

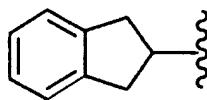
- (G) R³ is selected from aryl; heteroaryl; heterocycloalkyl; alkyl; or cycloalkyl; wherein said aryl or heteroaryl R³ groups is optionally substituted with 1 to 3 substituents independently selected from halogen; hydroxyl; lower alkoxy; -Oaryl; -SR²²; -CF₃; -OCF₃; -OCHF₂; -NR⁴R⁵; phenyl; -NO₂; -CO₂R⁴; -CON(R⁴)₂ wherein each
- 15 R⁴ is the same or different; -S(O)₂R²²; -S(O)₂N(R²⁰)₂ wherein each R²⁰ is the same or different; -N(R²⁴)S(O)₂R²²; -CN; -CH₂OH; -OCH₂CH₂OR²²; or alkyl;

- (H) R⁴ is selected from hydrogen; C₁-C₆ alkyl; cycloalkyl; cycloalkylalkyl; heterocycloalkylalkyl; bridged bicyclic cycloalkyl ring; aryl having a fused heterocycloalkyl ring bound to said aryl ring; aryl; arylalkyl; alkylaryl; -(CH₂)_dCH(R^{12A})₂
- 20 wherein d is 1 to 3, and each R^{12A} is independently selected from phenyl or substituted phenyl, said substituted phenyl being substituted with 1 to 3 substituents independently selected from: halogen, -Oalkyl, -OCF₃, -CF₃, -CN, or -NO₂; heterocycloalkylheteroaryl; or -(C₁ to C₆)alkylene-O-R²²;

- wherein the aryl R⁴ group, the aryl portion of the arylalkyl R⁴ group, or the aryl
- 25 portion of the alkylaryl R⁴ group is optionally substituted with 1 to 3 substituents independently selected from halogen; hydroxyl; lower alkyl; lower alkoxy; -CF₃; -N(R²⁰)(R²⁴); phenyl; -NO₂; -C(O)N(R²⁰)₂ (wherein each R²⁰ is the same or different); -C(O)R²²; -(CH₂)_k-cycloalkyl; -(CH₂)_q-aryl; or -(CH₂)_m-OR²²;

- (I) each R^{4B} is independently selected from: H, heteroaryl, alkyl, alkenyl, a
- 30 group of the formula

- 15 -



arylalkyl, or arylalkyl wherein the aryl moiety is substituted with 1-3 substituents independently selected from: halogen;

- (J) R^5 is selected from: hydrogen, C_1 - C_6 alkyl, $-C(O)R^{20}$, $-C(O)_2R^{20}$,
 5 $-C(O)N(R^{20})_2$ (wherein each R^{20} is the same or different);
- (K) each R^{10A} is independently selected from H or C_1 to C_6 alkyl, or each R^{10A} , taken together with the nitrogen atom to which they are bound, forms a 4 to 7 membered heterocycloalkyl ring;
- (L) R^{12} is selected from alkyl, hydroxyl, alkoxy, or fluoro, provided that when
 10 R^{12} is hydroxy or fluoro then R^{12} is not bound to a carbon adjacent to a nitrogen; or R^{12} forms an alkyl bridge from one ring carbon to another ring carbon;
- (M) R^{13} is selected from alkyl, hydroxyl, alkoxy, or fluoro, provided that when R^{13} is hydroxy or fluoro then R^{13} is not bound to a carbon adjacent to a nitrogen; or R^{13} forms an alkyl bridge from one ring carbon to another ring carbon;
- (N) R^{20} is selected from hydrogen, alkyl, or aryl, wherein said aryl group is
 15 optionally substituted with from 1 to 3 groups independently selected from: halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy; or when two R^{20} groups are present, said two R^{20} groups taken together with the nitrogen to which they are bound form a five or six membered heterocyclic ring;
- (O) R^{22} is selected from: heterocycloalkyl, alkyl or aryl, wherein said aryl
 20 group is optionally substituted with 1 to 3 groups independently selected from halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy;
- (P) R^{24} is selected from: hydrogen, alkyl, $-SO_2R^{22}$, or aryl, wherein said aryl
 group is optionally substituted with 1 to 3 groups independently selected from
 25 halogen, $-CF_3$, $-OCF_3$, hydroxyl, or methoxy;
- (Q) a is 0 to 2;
- (R) b is 0 to 2;
- (S) k is 1 to 5;
- (T) m is 2 to 5;
- (U) n is 1, 2 or 3 with the proviso that when M^1 is N, then n is not 1;
 30 (V) p is 1, 2 or 3 with the proviso that when M^2 is N, then p is not 1;

- 16 -

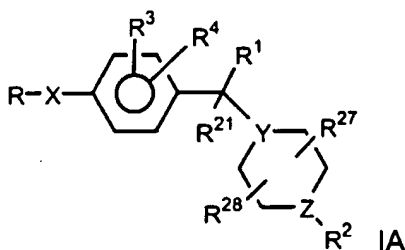
(W) q is 1 to 5; and

(X) r is 1, 2, or 3 with the proviso that when r is 2 or 3, M² is C and p is 1.

Other H₃ receptor antagonists can be identified by the test method
 5 described below.

Preferred H₃ antagonists are clobenpropit, impromidine, GT-2331, GR-175737, UCL-1199, and those disclosed in US 5,990,147, US Application No. 09/978,267 and US Provisional Application 60/275,417.

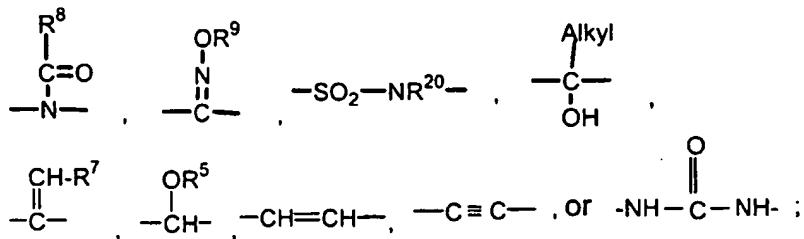
Muscarinic antagonists, in particular those having m₂ activity, are disclosed in
 10 several U.S. patents. US 5,883,096 and a divisional thereof, US 6,037,352, disclose the following compounds:



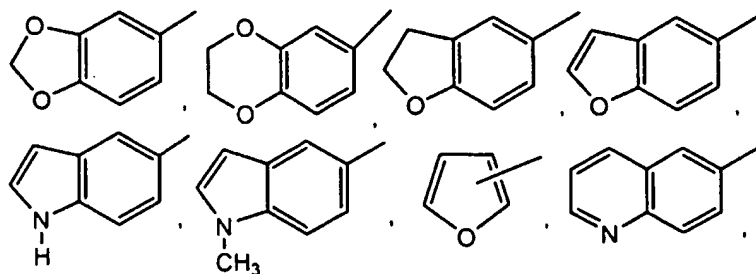
including all isomers and pharmaceutically acceptable salts, esters, and solvates thereof,

15 wherein one of Y and Z is N and the other is N, CH, or C-alkyl;

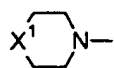
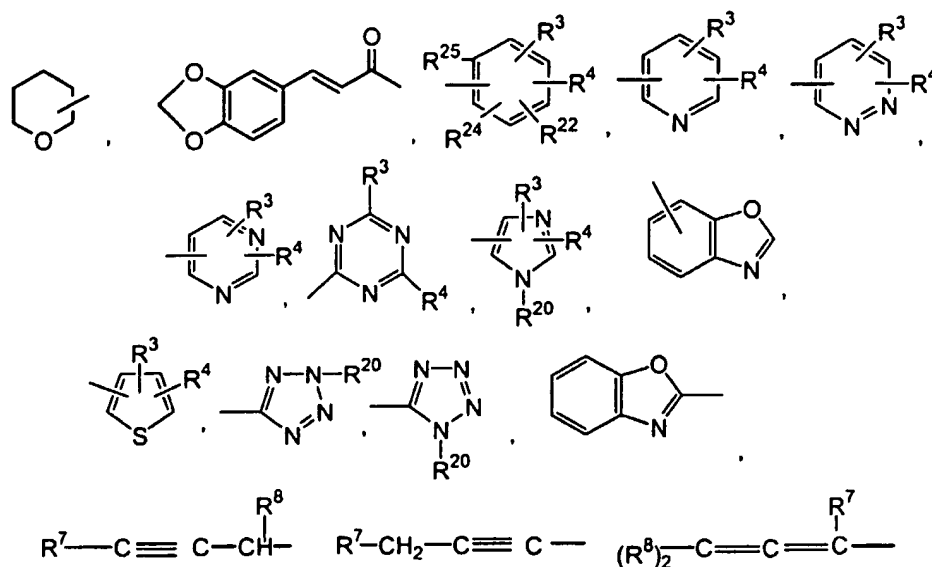
X is -O-, -S-, -SO-, -SO₂-, -NR⁶-, -CO-, -CH₂-, -CS-, -C(OR⁵)₂-, -C(SR⁵)₂-, -CONR²⁰-, -C(alkyl)₂-, -C(H)(alkyl)-, -NR²⁰-SO₂-, -NR²⁰CO-,



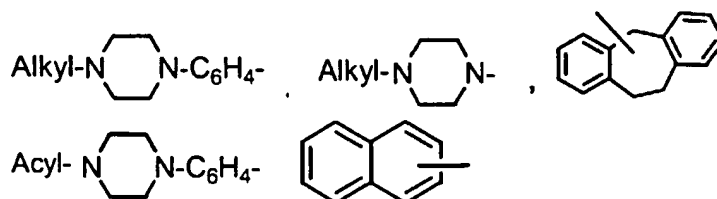
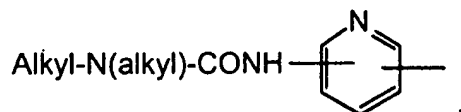
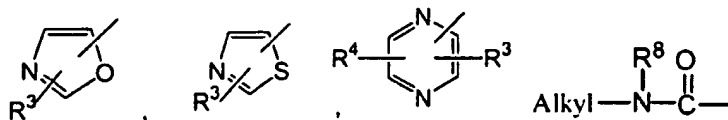
20 R is



- 17 -



(wherein X^1 is $-\text{CH}_2-$, $-\text{O}-$, or $-\text{NR}^7-$),

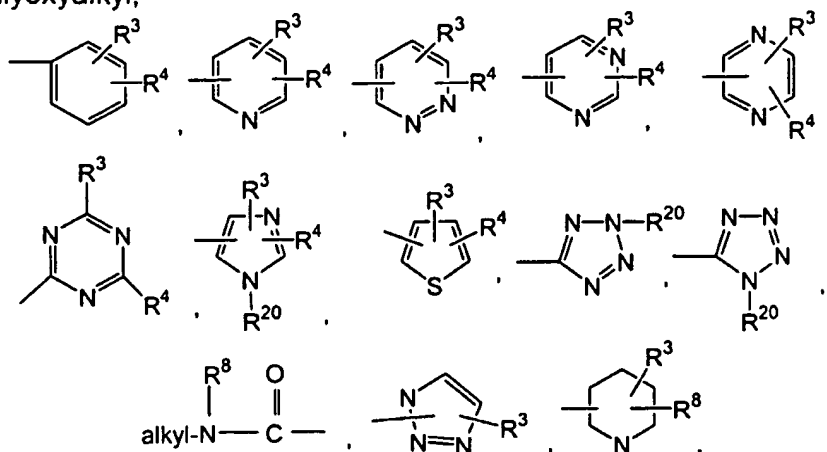


hydrogen, acyl, alkyl, alkenyl, cycloalkyl, cycloalkyl substituted with up to two alkyl groups, cycloalkenyl, bicycloalkyl, arylalkenyl, benzyl, benzyl substituted with up to three independently selected R³ groups, cycloalkylalkyl, polyhaloacyl, benzyloxyalkyl, hydroxyC₂-C₂₀alkyl, alkenylcarbonyl, alkylarylsulfonyl, alkoxy-carbonylaminoacyl, alkylsulfonyl, or arylsulfonyl, additionally, when X is -CH₂-, R may also be -OH; in further addition, when X is not N, R may also be hydroxymethyl, in further addition, R and X may combine to form the group Prot-(NOAA)_r-NH- wherein r is an integer of 1 to 4, Prot is a nitrogen protecting group and when r is 1, NOAA is a naturally occurring amino acid or an enantiomer thereof, or when r is 2 to 4, each NOAA is a peptide of an independently selected naturally occurring amino acid or an enantiomer thereof;

- 18 -

R¹ and R²¹ are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, bicycloalkyl, alkynyl, cyano, aminoalkyl, alkoxy carbonyl, aminocarbonyl, hydroxyguanidino, alkoxy carbonylalkyl, phenyl alkyl, alkylcarbonyloxyalkyl,

5



10

H, —OH, (provided R¹ and R²¹ are both not —OH and Y is not N), formyl, —CO alkyl, —COacyl, —COaryl, and hydroxyalkyl; additionally R¹ and R²¹ together may form the group

=CH_2 , =N-OR^5 , =N-CN , $\text{=N-N(R}^5\text{)}_2$, =CH-Alkyl , alkylene, =O , =C-Alkyl , =C(halo)_2 , in further addition, R¹ and R²¹ together with the carbon atom to which



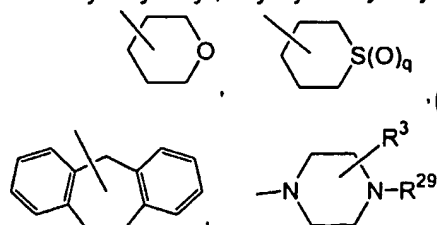
they are attached may form the group

15

or R¹ and R²¹ together with the carbon atom to which they are attached may form a saturated heterocyclic ring containing 3 to 7 carbon atoms and one group selected from S, O, and NH;

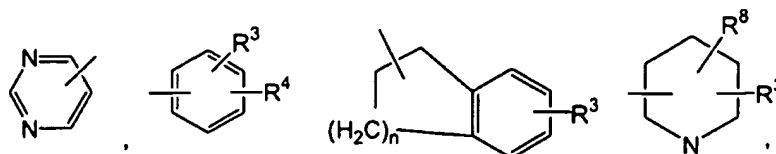
20

R² is H, alkyl, alkenyl, cycloalkyl, cycloalkyl substituted with 1 to 3 independently selected R³ groups, cycloalkenyl, hydroxyC₂-C₂₀alkyl, alkynyl, alkylamide, cycloalkylalkyl, hydroxyarylalkyl, bicycloalkyl, alkynyl, acylaminoalkyl, arylalkyl, hydroxyalkoxyalkyl, azabicyclo, alkylcarbonyl, alkoxyalkyl, aminocarbonylalkyl, alkoxy carbonylaminoalkyl, alkoxy carbonylamino(alkyl)alkyl; alkylcarbonyloxyalkyl, arylhydroxyalkyl, alkylcarbonylamino(alkyl)alkyl, dialkylamino,

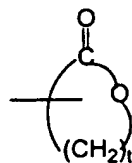
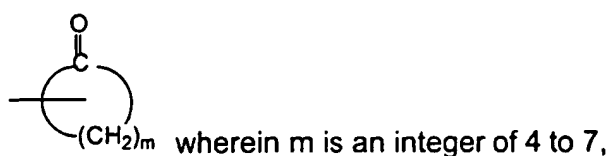


(wherein q is an integer of 0 to 2)

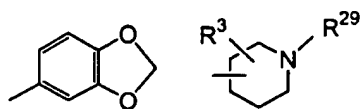
- 19 -



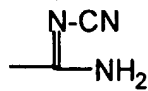
wherein n is 1-3



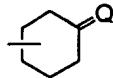
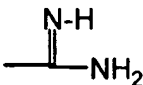
wherein t is an integer of 3 to 5,



- 5 (wherein R^{29} is H, alkyl, acyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylsulfonyl, arylsulfonyl),



or



(wherein Q is O, NOH, or NO-alkyl),

or when Z is -CH-, R^2 may also be alkoxycarbonyl, hydroxymethyl, -N(R^8)₂;

- 10 R^3 , R^4 , R^{22} , R^{24} , and R^{25} are independently selected from the group consisting of H, halo, alkoxy, benzyloxy, benzyloxy substituted by nitro or aminoalkyl, haloalkyl, polyhaloalkyl, nitro, cyano, sulfonyl, hydroxy, amino, alkylamino, formyl, alkylthio, polyhaloalkoxy, acyloxy, trialkylsilyl, alkylsulfonyl, arylsulfonyl, acyl, alkoxycarbonyl, alkylsulfinyl; -OCONH₂, -OCONH-alkyl, -OCON(alkyl)₂, -NHCOO-alkyl, -NHCO-alkyl, phenyl, hydroxyalkyl, or morpholino;

- 15 each R^5 and R^6 is independently selected from the group consisting of H and alkyl, provided that when X is C(OR⁵)₂ or C(SR⁵)₂, both R^5 groups cannot be H, and in addition, when X is C(OR⁵)₂ or C(SR⁵)₂, the two R^5 groups in X may be joined to form -(CH₂)_p- wherein p is an integer of 2 to 4;

- 20 R^7 is independently selected from the group consisting of H, alkyl, arylalkyl, cycloalkyl, aryl and aryl substituted with R^3 and R^4 as defined herein;

each R^8 is independently selected from the group consisting of H, hydroxyalkyl, or alkyl or two R^8 groups may be joined to form an alkylene group;

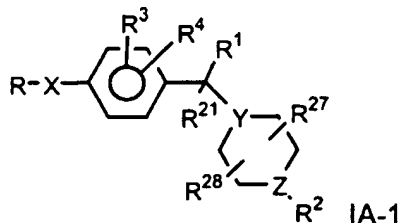
R^9 is H, alkyl, or acyl;

R^{20} is H, phenyl or alkyl; and

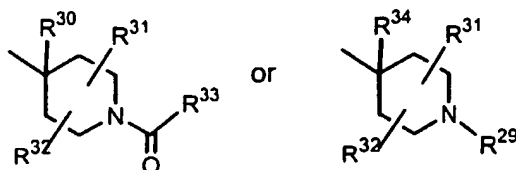
- 25 R^{27} and R^{28} are independently selected from the group consisting of H, alkyl, hydroxyalkyl, arylalkyl, aminoalkyl, haloalkyl, thioalkyl, alkylthioalkyl, carboxyalkyl, imidazolyalkyl, and indolyalkyl, additionally R^{27} and R^{28} may combine to form an alkylene group.

- 20 -

US 5,889,006 and a divisional thereof, US 6,043,255, disclose compounds of the formula



wherein R, R¹, R³, R⁴, R²¹, R²⁷, and R²⁸ are as described in US 5,883,096, but wherein R² is:



wherein

R²⁹ is H, alkyl, -CO-alkyl, alkoxycarbonyl, aminocarbonyl, aryloxy carbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylsulfonyl, or arylsulfonyl;

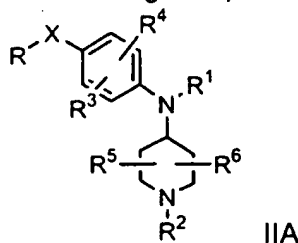
R³⁰ is H, alkyl, aryl, cycloalkyl, hydroxyalkyl, aminoalkyl, -COOR²⁰, -CON(R²⁰)₂ or cyano;

R³¹ and R³² are the same as R³⁰ and in addition, two R³⁰, R³¹ and R³² groups may form the group -(CH₂)_r- (wherein r is 1 to 6), in further addition, R³¹ and R³² can also be hydroxy, -N(R²⁰)₂, -O-acyl, -N(R²⁰)acyl, -OCOOR²⁰, or -OCON(R²⁰)₂;

R³³ is aryl or heteroaryl, with the proviso that when R³³ is heteroaryl, the CO-R³³ bond is to a carbon atom in the R³³ group; and

R³⁴ is alkyl, cycloalkyl or aryl and in addition R³⁴ may also be H when R¹ and R²¹ together with the carbon atom to which they are attached form a saturated heterocyclic ring containing 3 to 7 carbon atoms and two groups independently selected from S, O, and N-R²⁰.

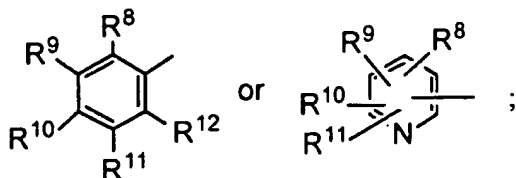
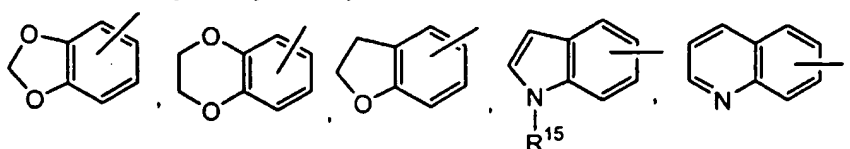
US 5,952,349 discloses the following compounds:



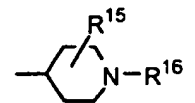
or an isomer, pharmaceutically acceptable salt, ester or solvate thereof, wherein

X is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -C(OR⁷)₂-, -CH₂-O-, -O-CH₂-, -CH=CH-, -CH₂-, -CH(C₁-C₆ alkyl)-, -C(C₁-C₆ alkyl)₂-, -CONR¹⁷-, -NR¹⁷CO-, -SO₂NR¹⁷- or -NR¹⁷SO₂-;

- 21 -

R is C₃-C₆ cycloalkyl,

5 R¹ is H, -CN, -CF₃, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, C₃-C₆ alkenyl, -COR¹⁵, -COO(C₁-C₆ alkyl), -COO(aryl), -COO(heteroaryl), -COO((C₁-C₆ alkyl)aryl), -COO((C₁-C₆ alkyl)heteroaryl), -(C₁-C₆ alkyl)aryl, -(C₁-C₆ alkyl)heteroaryl or -CON(R¹³)₂;

R² is C₃-C₆ cycloalkyl, C₃-C₆ cycloalkenyl, t-butoxycarbonyl or

10 R³ and R⁴ are independently selected from the group consisting of H, halo, -CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy and -OH;

R⁵ and R⁶ are independently selected from the group consisting of H, C₁-C₆ alkyl, -CF₃, C₁-C₆ alkoxy, -OH, C₁-C₆ alkylcarbonyl, C₁-C₆ alkoxy carbonyl, R¹³CONH-, R¹⁴OCONH-, R¹³NHCONH- and NH₂CONR¹³;

15 R⁷ is independently selected from the group consisting of H and alkyl, provided that both R⁷ groups are not H; or the two R⁷ groups may be joined to form -(CH₂)_p- wherein p is an integer of 2 to 4;

20 R⁸, R⁹, R¹⁰, R¹¹ and R¹² are independently selected from the group consisting of H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, benzyloxy, benzyloxy substituted by -NO₂ or -N(R¹⁴), halo C₁-C₆ alkyl, polyhalo C₁-C₆ alkyl, -NO₂, -CN, -SO₂, -OH, -NH₂, -N(R¹⁴)₂, -HCO, polyhalo C₁-C₆ alkoxy, acyloxy, (C₁-C₄ alkyl)₃Si-, (C₁-C₆ alkyl)SO₂, arylsulfonyl, heteroaryl-sulfonyl, acyl, (C₁-C₆ alkoxy)CO-, -OCON(R¹⁴)₂, -NHCOO-(C₁-C₆)alkyl, -NHCO-(C₁-C₆ alkyl), phenyl, hydroxy(C₁-C₆ alkyl) or morpholino;

25 R¹³ is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, -(C₁-C₆ alkyl)COOR¹⁵, aryl, heteroaryl, -(C₁-C₆ alkyl)aryl, -(C₁-C₆ alkyl)heteroaryl and adamantyl;

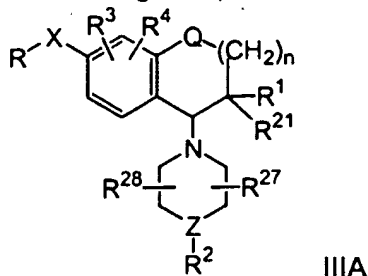
R¹⁴ is independently selected from the group consisting of H and C₁-C₆ alkyl;R¹⁵ is H, C₁-C₂₀ alkyl, C₁-C₆ cycloalkyl, aryl or heteroaryl;

R¹⁶ is H, C₁-C₆ alkyl, -COR¹⁵, C₁-C₆ alkoxy carbonyl, (R¹⁴)₂NCO- or -SO₁₋₂-R¹⁵; and

30 R¹⁷ is H, C₁-C₆ alkyl, aryl or heteroaryl.

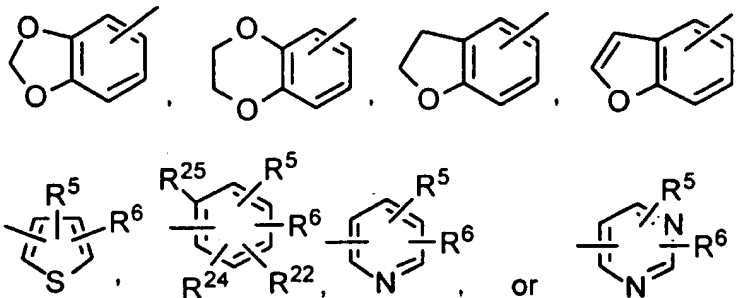
- 22 -

US 5,935,958 discloses the following compounds:



including all stereoisomers and pharmaceutically acceptable salts, esters, and solvates thereof, wherein:

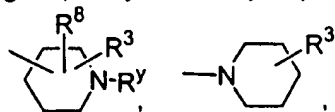
- 5 Z is N, CH or C-alkyl;
 X is -O-, -S-, -SO-, -SO₂-, -CO-, -CH₂-, -CONR²⁰-, -NR²⁰-SO₂-,
 -NR²⁰CO-, or -SO₂-NR²⁰-;
 Q is -O-, -S-, -SO-, -SO₂-, or -CH₂-;
 R is



10

R¹ and R²¹ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkenylalkyl, phenylalkyl, and hydroxyalkyl;

- 15 R² is cycloalkyl, cycloalkyl substituted with 1 to 3 independently selected R³ groups, cycloalkenyl, cycloalkylalkyl,



(wherein R⁹ is H, alkyl, alkenyl, SO₂R^z or COR^z wherein R^z is alkyl, alkenyl, aryl, heteroaryl, or cycloalkyl), with the proviso that R² is R³-substituted-1-piperidiny only when Z is CH or C-alkyl; or, when Z is CH, R² may also be alkoxycarbonyl, -N(R⁹)(hydroxyalkyl) wherein R⁹ is H, hydroxyalkyl, or alkyl, or -N(R⁹)₂ wherein the two R⁹ groups may be joined to form an alkylene group;

20

R³, R⁴, R⁵, R⁶, R²², R²⁴, and R²⁵ are independently selected from the group consisting of H, alkyl, halo, alkoxy, benzyloxy, benzyloxy substituted by nitro or aminoalkyl, polyhaloalkyl, nitro, sulfonyl, hydroxy, amino, alkylamino, formyl, alkylthio, acyloxy, alkylsulfonyl, arylsulfonyl, acyl, alkoxycarbonyl, alkylsulfinyl, -OCONH₂, -

- 23 -

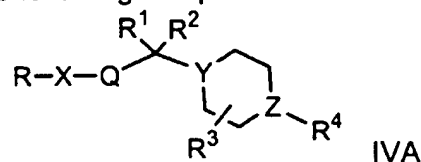
CONH-alkyl, -CON(alkyl)₂, -NHCOO-alkyl, -NHCO-alkyl, phenyl, hydroxyalkyl, and 1-morpholinyl;

R⁸ is hydrogen, lower alkyl or cyclopropyl;

R²⁰ is H, phenyl or alkyl;

- 5 R²⁷ and R²⁸ are independently selected from the group consisting of H, alkyl, hydroxyalkyl, alkoxyalkyl, arylalkyl, mercaptoalkyl, alkylthioalkyl, and carboxyalkyl, and additionally R²⁷ and R²⁸ may be joined to form an alkylene group; and n is 0 or an integer from 1 to 3.

US 6,066,636 discloses the following compounds:



10

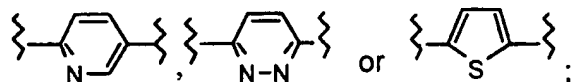
including all stereoisomers and pharmaceutically acceptable salts and solvates thereof,

wherein one of Y and Z is -N- and the other is -N- or -CH-;

X is -O-, -S-, -SO-, -SO₂- or -CH₂-;

15

Q is

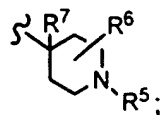


R is (C₁-C₂₀)alkyl, (C₃-C₁₂)cycloalkyl, aryl, R⁸-aryl or heteroaryl;

R¹, R² and R³ are independently selected from the group consisting of H and (C₁-C₂₀)alkyl;

20

R⁴ is (C₁-C₂₀)alkyl, (C₃-C₁₂)cycloalkyl or



R⁵ is H, (C₁-C₂₀)alkyl, -C(O)(C₁-C₂₀)alkyl, R⁹-arylcarbonyl, -SO₂(C₁-C₂₀)alkyl, R⁹-arylsulfonyl -C(O)O(C₁-C₂₀)alkyl, R⁹-aryloxy-carbonyl, -C(O)NH-(C₁-C₂₀)alkyl or R⁹-arylaminocarbonyl;

25

R⁶ is H or (C₁-C₂₀)alkyl;

R⁷ is H, (C₁-C₂₀)alkyl, hydroxy(C₁-C₂₀)alkyl or (C₁-C₂₀)-alkoxy(C₁-C₂₀)alkyl;

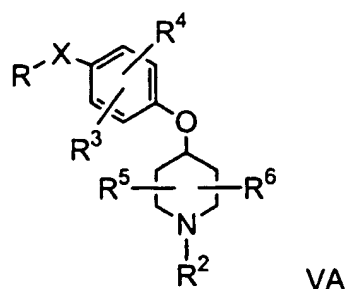
R⁸ is 1-3 substituents independently selected from the group consisting of H, (C₁-C₂₀)alkyl, halogen, hydroxy, (C₁-C₂₀)alkoxy or hydroxy(C₁-C₂₀)alkyl, or two adjacent R⁸ groups may be joined to form a (C₁-C₂)alkylenedioxy group; and

30

R⁹ is 1-3 substituents independently selected from the group consisting of H, (C₁-C₂₀)alkyl, halogen, amino or (C₁-C₂₀)alkylamino.

US 5,977,138 discloses the following compounds:

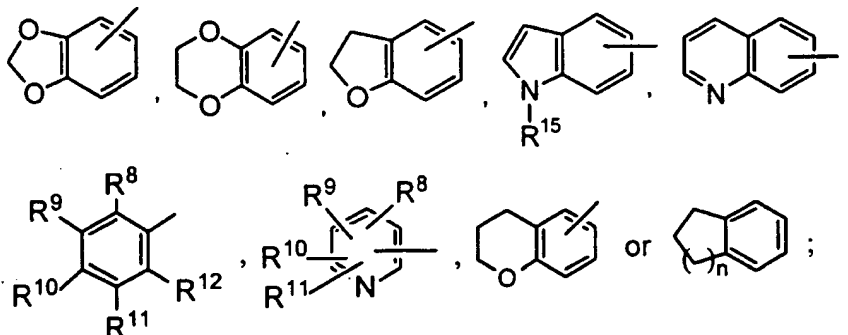
- 24 -



or an isomer, pharmaceutically acceptable salt, ester or solvate thereof, wherein

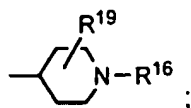
X is a bond, -O-, -S-, -SO-, -SO₂-, -CO-, -C(OR⁷)₂-, -CH₂-O-, -O-CH₂-, -CH=CH-, -CH₂-, -CH(C₁-C₆ alkyl)-, -C(C₁-C₆ alkyl)₂-, -CONR¹⁷-, -NR¹⁷CO-, -O-C(O)NR¹⁷-, -NR¹⁷C(O)-O-, -SO₂NR¹⁷- or -NR¹⁷SO₂-;

R is C₃-C₆ cycloalkyl,



n is 1, 2 or 3;

R² is H, C₂-C₇ alkyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyl substituted by 1 to 4 groups independently selected from R¹⁸, C₃-C₆ cycloalkenyl, t-butoxycarbonyl or



R³ and R⁴ are independently selected from the group consisting of H, halo, -CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy and -OH;

R⁵ and R⁶ are independently selected from the group consisting of H, C₁-C₆ alkyl, -CF₃, C₁-C₆ alkoxy, -OH, C₁-C₆ alkylcarbonyl, C₁-C₆ alkoxycarbonyl, R¹³CONH-, (R¹³)₂NCO-, R¹³OCONH-, R¹³NHCONH- and NH₂CONR¹³-;

R⁷ is independently selected from the group consisting of C₁-C₆ alkyl; or the two R⁷ groups may be joined to form -(C(R¹⁴)₂)_p- wherein p is an integer from 2-4;

R⁸, R⁹, R¹⁰, R¹¹ and R¹² are independently selected from the group consisting of H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, benzyloxy, benzyloxy substituted by -NO₂ or -N(R¹⁴), halo C₁-C₆ alkyl, polyhalo C₁-C₆ alkyl, -NO₂, -CN, -SO₂, -OH, -NH₂, -N(R¹⁴)₂, -CHO, polyhalo C₁-C₆ alkoxy, acyloxy, (C₁-C₄ alkyl)₃Si-, (C₁-C₆ alkyl)SO₀₋₂.

- 25 -

arylsulfonyl, heteroaryl-sulfonyl, acyl, (C₁-C₆ alkoxy)CO-, -OCON(R¹⁴)₂, -NHCOO-(C₁-C₆)alkyl, -NHCO-(C₁-C₆ alkyl), phenyl, hydroxy(C₁-C₆ alkyl) or morpholino;

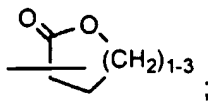
R¹³ is independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, -(C₁-C₆ alkyl)COOR¹⁵, aryl, heteroaryl, -(C₁-C₆ alkyl)aryl,

5 -(C₁-C₆ alkyl)heteroaryl and adamantyl;

R¹⁴ is independently selected from the group consisting of H and C₁-C₆ alkyl;

R¹⁵ is independently selected from the group consisting of H, C₁-C₂₀ alkyl, C₃-C₆ cycloalkyl, aryl substituted by 1 to 3 groups independently selected from R³ and heteroaryl substituted by 1 to 3 groups independently selected from R³;

10 R¹⁶ is H, C₁-C₆ alkyl, -COR²⁰, C₁-C₆ alkoxy, -CON(R¹⁴)₂, -CONH(R³-

aryl), -SO₁₋₂-R¹⁵, -SO₁₋₂-(CH₂)_m-R²¹, -SON(R¹⁴)₂, -COSR¹⁴ or  ;

R¹⁷ is H, C₁-C₆ alkyl, aryl or heteroaryl;

R¹⁸ is independently selected from the group consisting of halo, -CF₃, C₁-C₆ alkyl, C₁-C₆ alkoxy, -OH, =O, -CON(R¹⁴)₂ and -N(R¹⁴)COR¹⁵;

15 R¹⁹ is H, -OH, C₁-C₂₀ alkyl, C₃-C₆ cycloalkyl, aryl substituted by 1 to 3 groups independently selected from R³ or heteroaryl substituted by 1 to 3 groups independently selected from R³;

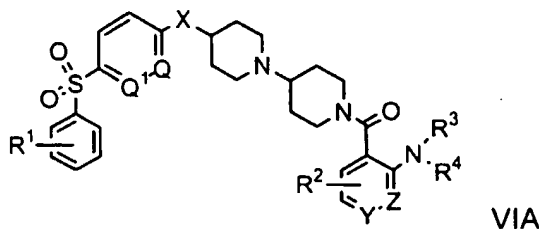
R²⁰ is H, C₁-C₂₀ alkyl, C₁-C₆ alkoxy(C₁-C₆)alkyl, C₃-C₆ cycloalkyl, aryl, aryl(C₁-C₆ alkyl)-, aryloxy, aryloxy(C₁-C₆ alkyl)-, tetrahydrofuranyl or heteroaryl,

20 wherein the aryl or heteroaryl group is substituted by 1 to 3 groups independently selected from R³;

m is 0 to 3; and

R²¹ is C₇-C₁₀ bridged cycloalkyl or C₇-C₁₀ bridged cycloalkyl wherein the cycloalkyl portion is substituted by 1 or 2 substituents selected from the group
25 consisting of C₁-C₆ alkyl or =O.

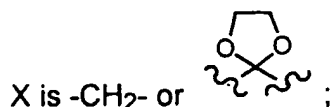
A genus of selective m₂ muscarinic antagonists, disclosed in US 6,294,554 B1, has the following structural formula:



30 or a pharmaceutically acceptable salt, ester or solvate thereof, wherein

Q and Q¹ are each -CH=, or one of Q and Q¹ is -CH= and the other is -N=;

- 26 -



Y and Z are independently selected from the group consisting of -C(R⁵)=, or one of Y and Z is -C(R⁵)= and the other is -N=;

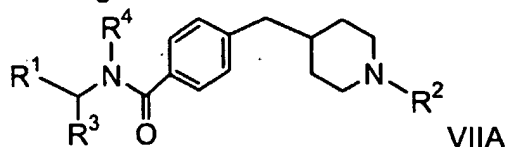
R¹ is 1 to 3 substituent independently selected from the group consisting of H, halogen and (C₁-C₆)alkoxy;

R² and R⁵ are independently 1 to 3 substituents independently selected from the group consisting of H, halogen, (C₁-C₆)alkyl and (C₁-C₆)alkoxy; and

R³ and R⁴ are independently selected from the group consisting of H and (C₁-C₆)alkyl.

Of those compounds, preferred are compounds wherein both Y and Z are -C(R⁵)=, and wherein R⁵ is preferably H, methyl or halogen. Also preferred are compounds wherein Y is -CH=, Z is -N= and R² is hydrogen. R¹ is preferably halogen, more preferably chloro, or methoxy, and in particular, R¹ is 3-chloro or 4-methoxy. Q and Q¹ are preferably each -CH=. Preferred R² substituents are Cl, F and methyl, with 3-methyl being more preferred. R³ and R⁴ are preferably each H.

US Provisional Application No. 60/257,853, filed December 22, 2000 discloses compounds having the following structure:



or a pharmaceutically acceptable salt, ester or solvate thereof, wherein

R¹ is R⁵-(C₃-C₈)cycloalkyl, R⁵-(C₃-C₈)cycloalkyl(C₁-C₆)alkyl, R⁵-aryl, R⁵-aryl-(C₁-C₆)alkyl or R⁵-heteroaryl;

R² is H, (C₁-C₆)alkyl, R⁶-(C₃-C₈)cycloalkyl, R⁶-(C₃-C₈)cycloalkyl-(C₁-C₆)alkyl, R⁶-heterocycloalkyl, R⁶-(C₆-C₁₀)bridged cycloalkyl, or R⁶-bridged heterocycloalkyl;

R³ is C₁-C₆ alkyl or -CH₂OH;

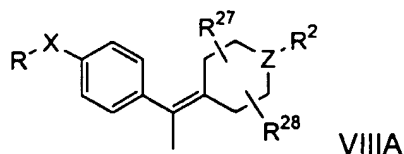
R⁴ is H or C₁-C₆ alkyl;

R⁵ is 1-4 substituents independently selected from the group consisting of H, C₁-C₆ alkyl, halogen, -OH, C₁-C₆ alkoxy, CF₃, -CN, -CO₂R⁴, -CONHR⁴, -SO₂NHR⁴, -NHSO₂R⁴ and -NHC(O)R⁴; and

R⁶ is 1-4 substituents independently selected from the group consisting of H, C₁-C₆ alkyl, halogen, -OH, C₁-C₆ alkoxy, CF₃, -NH₂, (C₁-C₆)alkylamino, phenyl, C₁-C₂ alkylenedioxy, and (C₁-C₆)alkoxycarbonyl.

US Provisional Application No. 60/328,356, filed October 10, 2001 discloses compounds having the following structure:

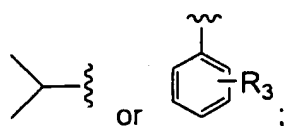
- 27 -



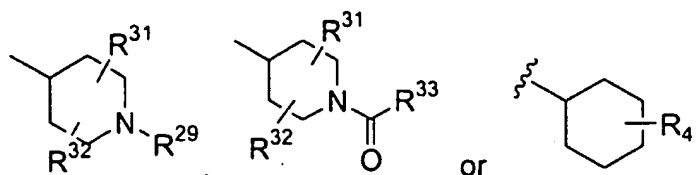
including enantiomers, stereoisomers, rotamers, tautomers and prodrugs of said compound, or pharmaceutically acceptable salts, esters or solvates of said compound or of said prodrugs, wherein:

- 5 Z is N, CH, or C-alkyl;
 X is -O-, -S-, -SO-, -SO₂-, -CO-, -CH₂-, or -CS;

R is



R² is



10

R³ is alkoxy or halo;

R⁴ is hydrogen, alkyl or alkylhalide;

- 15 R²⁷ and R²⁸ are independently selected from the group consisting of H, alkyl, hydroxyalkyl, arylalkyl, aminoalkyl, haloalkyl, thioalkyl, alkylthioalkyl, carboxyalkyl, imidazolyalkyl, and indolyalkyl; or R²⁷ and R²⁸ may combine to form an alkylene group;

R²⁹ is H, alkyl, -CO-alkyl, -CO-cycloalkyl, alkoxy-carbonyl, amino-carbonyl, aryloxy-carbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylsulfonyl, arylsulfonyl or -SO₂-NH-R³⁵;

- 20 R³¹ and R³² are each independently H, alkyl, aryl, cycloalkyl, hydroxyalkyl, or aminoalkyl, and in addition, R³¹ and R³² can form the group -(CH₂)_r (wherein r is 1 to 6), in further addition, R³¹ and R³² can also be hydroxy, -N(R³⁵)₂, -O-acyl, -N(R³⁵)acyl, -OCOOR³⁵, or -OCON(R³⁵)₂;

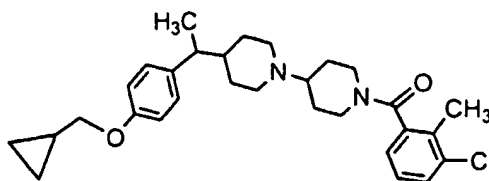
R³³ is aryl or heteroaryl, with the proviso that when R³³ is heteroaryl, the CO-R³³ bond is to a carbon atom in the R³³ group; and

- 25 R³⁵ is H, aryl or alkyl.

Preferred m₂ antagonists are those claimed in US patent 6,043,255.

An especially preferred m₂ antagonist has the structure

- 28 -



The US patents and applications cited herein are incorporated herein by reference.

Other m_2 antagonists can be identified by the test methods described below.

5 The H_3 antagonist and m_2 antagonist compounds are prepared by known methods. The dual H_3 / m_2 antagonists listed above are prepared by methods described in the m_2 antagonist patents listed above.

The combination of H_3 and m_2 antagonists can also comprise more than one H_3 antagonist (e.g., 2-3) and/or more than one m_2 antagonist (e.g., 2-3).

10 In the aspect of the invention relating to a combination of a dual H_3/m_2 antagonist in combination with an acetylcholinesterase inhibitor, or a combination of an H_3 antagonist and a m_2 antagonist with an acetylcholinesterase inhibitor, examples of acetylcholinesterase inhibitors are donepezil, heptylphysostigmine, tacrine, rivastigmine and galantamine.

15

Test Methods:

Compounds can readily be evaluated to determine activity at H_3 receptors by known methods, including the guinea pig brain membrane assay and the guinea pig neurogenic ileum contraction assay, both of which are
20 described in U.S. Patent 5,352,707. Another useful assay utilizes rat brain membranes and is described by West et al., "Identification of Two H_3 -Histamine Receptor Subtypes," *Molecular Pharmacology*, Vol. 38, pages 610-613 (1990).

25 A particularly useful screening assay measures binding to sites in guinea pig brain membranes. This test is described in detail by Korte et al., "Characterization and Tissue Distribution of H_3 Histamine Receptors in Guinea Pigs by N^a -Methylhistamine," in *Biochemical and Biophysical Research Communications*, Vol. 168, pages 979-986 (1990), and quantifies the displacement of bound radiolabeled N^a -methylhistamine from tissues by
30 candidate compounds. Results are expressed as " K_i " values, in nanoMolar (nM) units, which values can be considered as being dissociation constants for the H_3 antagonist on the H_3 receptor system, or an index of antagonist affinity for the receptor. In general, K_i values less than about 200 nM are

- 29 -

considered necessary for an agent to be useful as an H₃ antagonist in the invention. More preferably, the agent will exhibit K_i values of 100 nM or less.

The compound of interest also is tested for its ability to inhibit binding to the cloned human m₁, m₂ and m₄ muscarinic receptor subtypes. The sources of receptors
 5 in these studies were membranes from stably transfected CHO cell lines which were expressing each of the receptor subtypes. Following growth, the cells were pelleted and subsequently homogenized using a Polytron in 50 volumes cold 10 mM Na/K phosphate buffer, pH 7.4 (Buffer B). The homogenates were centrifuged at 40,000 x g for 20 minutes at 4°C. The resulting supernatants were discarded and the pellets
 10 were resuspended in Buffer B at a final concentration of 20 mg wet tissue/ml. These membranes were stored at -80°C until utilized in the binding assays described below.

Binding to the cloned human muscarinic receptors was performed using ³H-quinuclidinyl benzilate (QNB) (Watson et al., 1986). Briefly, membranes (approximately 8, 20, and 14 µg of protein assay for the m₁, m₂, and m₄ containing
 15 membranes, respectively) were incubated with ³H-QNB (final concentration of 100-200 pM) and increasing concentrations of unlabeled drug in a final volume of 2 ml at 25°C for 90 minutes. Non-specific binding was assayed in the presence of 1 µM atropine. The incubations were terminated by vacuum filtration over GF/B glass fiber filters using a Skatron filtration apparatus and the filters were washed with cold 10mM
 20 Na/K phosphate butter, pH 7.4. Scintillation cocktail was added to the filters and the vials were incubated overnight. The bound radioligand was quantified in a liquid scintillation counter (50% efficiency). The resulting data were analyzed for IC₅₀ values (i.e. the concentration of compound required to inhibit binding by 50%) using the EBDA computer program (McPherson, 1985).

25 Affinity values (K_i) are determined using the following formula;

$$K_i = \frac{IC_{50}}{1 + \left[\frac{\text{concentration of radioligand}}{\text{affinity (K}_D\text{) of radioligand}} \right]}$$

Hence, a lower value of K_i indicates greater binding affinity.

To determine the degree of selectivity of a compound for binding the m₂ receptor, the K_i value for m₁ receptors was divided by the K_i value for m₂ (or m₄)
 30 receptors. A higher ratio indicates a greater selectivity for binding the m₂ muscarinic receptor.

The following procedure is used to show that a compound functions as a m₂ antagonist.

Surgery: For these studies, male Sprague-Dawley Rats (250-350 g) were
 35 anesthetized with sodium pentobarbital (54 mg/kg, ip) and placed on a Kopf stereotaxic

- 30 -

apparatus. The skull was exposed and drilled through to the dura at a point 0.2 mm anterior and 3.0 mm lateral to the bregma. At these coordinates, a guide cannula was positioned at the outer edge of the dura through the drilled opening, lowered perpendicularly to a depth of 2.5 mm, and permanently secured with dental cement to bone screws. Following the surgery, rats were given ampicillin (40 mg/kg, ip) and individually housed in modified cages. A recovery period of approximately 3 to 7 days was allowed before the microdialysis procedure was undertaken.

Microdialysis: All of the equipment and instrumentation used to conduct in vivo microdialysis was obtained from Bioanalytical Systems, Inc. (BAS). The microdialysis procedure involved the insertion through the guide cannula of a thin, needle-like perfusable probe (CMA/12,3 mm x 0.5 mm) to a depth of 3 mm in striatum beyond the end of the guide. The probe was connected beforehand with tubing to a microinjection pump (CMA/ 100). Rats were collared, tethered, and, following probe insertion, were placed in a large, clear, plexiglass bowl with litter material and access to food and water. The probe was perfused at 2 µl/min with Ringer's buffer (NaCl 147 mM; KCl 3.0 mM; CaCl₂ 1.2 mM; MgCl₂ 1.0 mM) containing 5.5 mM glucose, 0.2 mM L-ascorbate, and 1 µM neostigmine bromide at pH 7.4). To achieve stable baseline readings, microdialysis was allowed to proceed for 90 minutes prior to the collection of fractions. Fractions (20 µl) were obtained at 10 minute intervals over a 3 hour period using a refrigerated collector (CMA/170 or 200). Four to five baseline fractions were collected, following which the drug or combination of drugs to be tested was administered to the animal. Upon completion of the collection, each rat was autopsied to determine accuracy of probe placement.

Acetylcholine (ACh) analysis: The concentration of ACh in collected samples of microdialysate was determined using HPLC/electrochemical detection. Samples were auto-injected (Waters 712 Refrigerated Sample Processor) onto a polymeric analytical HPLC column (BAS, MF-6150) and eluted with 50 mM Na₂HPO₄, pH 8.5. To prevent bacterial growth, Kathon CG reagent (0.005%) (BAS) was included in the mobile phase. Eluent from the analytical column, containing separated ACh and choline, was then immediately passed through an immobilized enzyme reactor cartridge (BAS, MF-6151) coupled to the column outlet. The reactor contained both acetylcholinesterase and choline oxidase covalently bound to a polymeric backbone. The action of these enzymes on ACh and choline resulted in stoichiometric yields of hydrogen peroxide, which was electrochemically detected using a Waters 460 detector equipped with a platinum electrode at a working potential of 500 mvolts. Data acquisition was carried out using an IBM Model 70 computer equipped with a microchannel IEEE board. Integration and quantification of peaks were accomplished using "Maxima" chromatography software (Waters Corporation). Total run time per

- 31 -

sample was 11 minutes at a flow rate of 1 ml/min. Retention times for acetylcholine and choline were 6.5 and 7.8 minutes, respectively. To monitor and correct for possible changes in detector sensitivity during chromatography, ACh standards were included at the beginning, middle and end of each sample queue.

- 5 Increases in ACh levels are consistent with presynaptic m_2 receptor antagonism.

Affinity values for the H_3 and m_2 receptors were determined for the dual antagonists identified above. The results of the test procedures are as follows:

Compound Number	H_3 Ki	m_2 Ki
1	18	0.17
2	140	0.01
3	500	0.125
4	620	3.4
5	430	2.6
6	160	1.2
7	22	0.07
8	6	0.05
9	290	0.22
10	15	0.019
11	8	0.018
12	170	4.8
13	12	0.8
14	2	0.7
15	43	0.17

10

- For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

- 20 For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed

- 32 -

homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound or combination is administered orally.

Preferably, the pharmaceutical preparation comprising a dual H_3/m_2 antagonist is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active dual H_3/m_2 antagonist compound in a unit dose of preparation may be varied or adjusted from about 1 mg to 100 mg, preferably from about 1 mg. to 50 mg, more preferably about 1 to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the dual compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen for dual H_3/m_2 antagonist is oral administration

- 33 -

of from 1 mg to 300 mg/day, preferably 1 to 50 mg/day, in two to four divided doses to provide relief from cognition deficit disorders such as Alzheimer's disease.

When the invention comprises a combination of separate H_3 antagonist and m_2 antagonist compounds, the two active components may be co-administered simultaneously or sequentially, or a single pharmaceutical composition comprising a H_3 antagonist and an m_2 antagonist in a pharmaceutically acceptable carrier can be administered. The components of the combination can be administered individually or together in any conventional dosage form such as capsule, tablet, powder, cachet, suspension, solution, suppository, nasal spray, etc. The dosage of the H_3 antagonist can be determined from published material, and may range from 1 to 1000 mg per dose. The m_2 antagonist can be administered in a dosage range of 1 mg to about 100 mg, preferably from about 1 mg. to 50 mg, and more preferably about 1 to about 25 mg. When used in combination, the dosage levels of the individual components are preferably lower than the recommended individual dosages because of the advantageous effect of the combination.

The dosage of the acetylcholinesterase inhibitor used in a combination may range from 0.001 to 100 mg/kg body weight.

When separate H_3 and m_2 pharmaceutical compositions are to be administered, they can be provided in a kit comprising in a single package, one container comprising an H_3 antagonist in a pharmaceutically acceptable carrier, and a separate container comprising a m_2 antagonist in a pharmaceutically acceptable carrier, with the H_3 and m_2 antagonists being present in amounts such that the combination is effective to treat cognition deficit disorders. When an acetylcholinesterase inhibitor is also administered, a separate container comprising an acetylcholinesterase inhibitor in a pharmaceutically acceptable carrier can also be added to the kit. A kit is advantageous for administering a combination when, for example, the components must be administered at different time intervals or when they are in different dosage forms.

The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a dual compound of the invention, although those skilled in the art will recognize that similar dosage forms will be suitable for separate H_3 and m_2 antagonists, or for combinations of the separate actives. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

35

- 34 -

Pharmaceutical Dosage Form ExamplesEXAMPLE A-Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	<u>3</u>	<u>7</u>
Total		300	700

Method of Manufacture

- Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B-Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	<u>7</u>	<u>7</u>
Total		253	700

Method of Manufacture

- Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

- While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

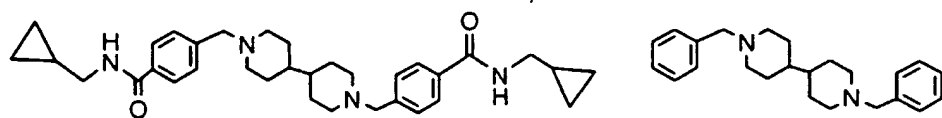
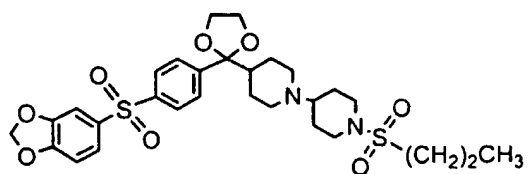
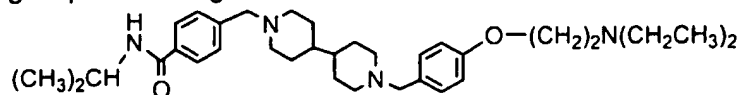
- 35 -

We claim:

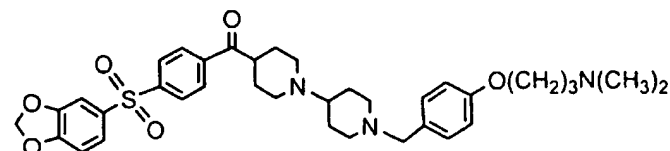
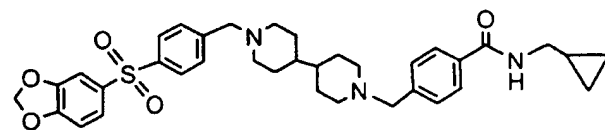
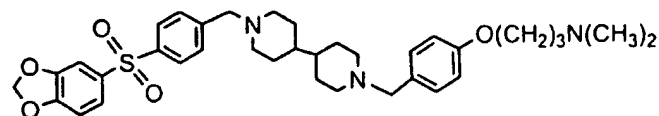
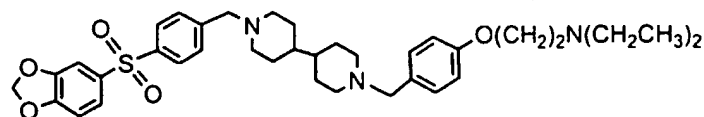
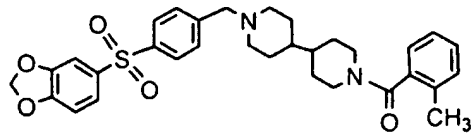
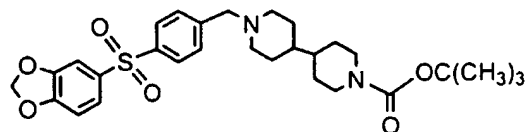
1. The use of a dual histamine H_3 receptor antagonist / m_2 muscarinic antagonist for the preparation of a medicament for the treatment of cognition deficit disorders.

5

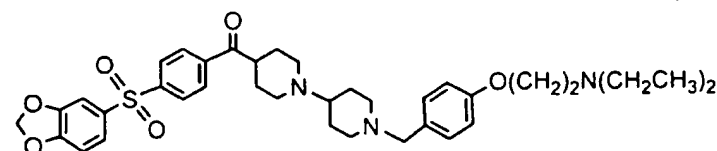
2. The use of claim 1 wherein the dual H_3/m_2 antagonist is selected from the group consisting of



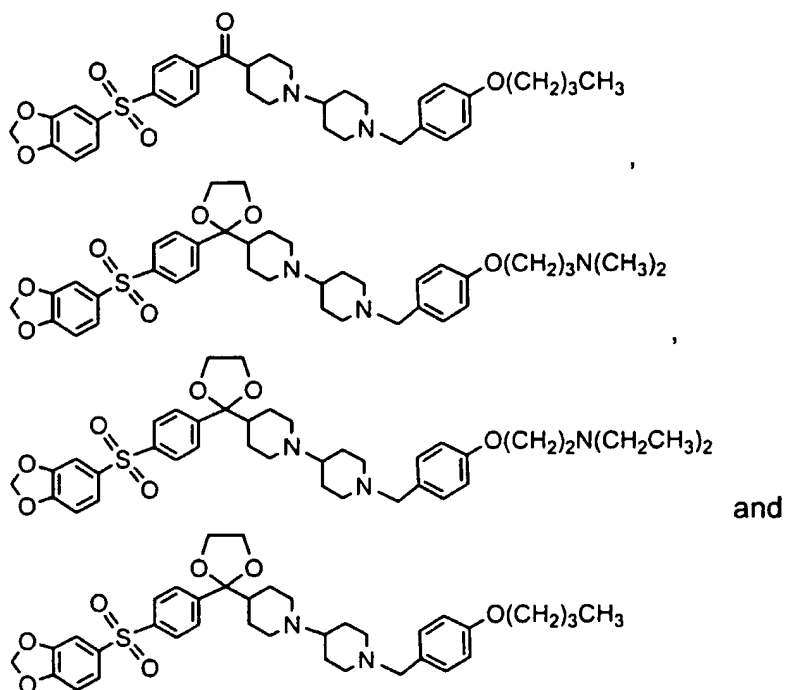
10



15



- 36 -



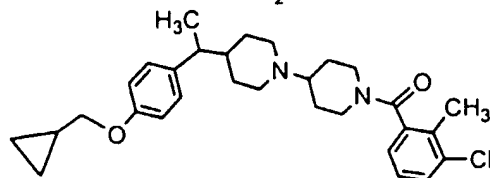
5

3. The use of treating a combination of an histamine H₃ receptor antagonist and a m₂ muscarinic antagonist for the preparation of a medicament for the treatment of cognition deficit disorders.

10 4. The use of claim 3 wherein the histamine H₃ receptor antagonist is selected from the group consisting of thioperamide, impromidine, burimamide, clobenpropit, impentamine, mifetidine, S-sopromidine, R-sopromidine, ciproxifam, SKF-91486, GR-175737, GT-2016, GT-2331, UCL-1199, clozapine and those of formula VIII or IX, and the m₂ muscarinic antagonist is selected from the compounds of the formula IA-1.

15

5. The use of claim 3 or 4 wherein the m₂ muscarinic antagonist is

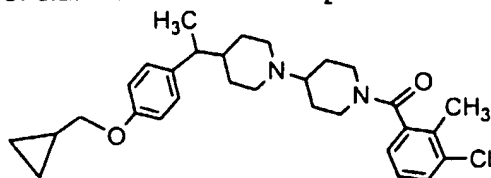


20 6. A pharmaceutical composition comprising an effective amount of a combination of a histamine H₃ antagonist and a m₂ muscarinic antagonist, and a pharmaceutically acceptable carrier.

- 37 -

7. The composition of claim 6 wherein the histamine H₃ receptor antagonist is selected from the group consisting of thioperamide, impromidine, burimamide, clobenpropit, impentamine, mifetidine, S-sopromidine, R-sopromidine, ciproxifam, SKF-91486, GR-175737, GT-2016, GT-2331, UCL-1199, clozapine and those of formula VIII or IX; and wherein the m₂ muscarinic antagonist is selected from the compounds of formula IA-1.

8. The composition of claim 7 wherein the m₂ muscarinic antagonist is



10

9. A kit comprising in a single package, one container comprising a histamine H₃ antagonist in a pharmaceutically acceptable carrier, and a separate container comprising a m₂ muscarinic antagonist in a pharmaceutically acceptable carrier, with the H₃ and m₂ antagonists being present in amounts such that the combination is effective to treat cognition deficit disorders.

10. The use of a dual histamine H₃ antagonist/m₂ muscarinic antagonist or an effective amount of a combination of a histamine H₃ receptor antagonist and a m₂ muscarinic antagonist, in combination with an effective amount of an acetylcholinesterase inhibitor, for the preparation of a medicament for the treatment of cognition deficit disorders.

11. A pharmaceutical composition comprising an effective amount of a dual histamine H₃ antagonist/ m₂ muscarinic antagonist or a combination of a histamine H₃ antagonist and a m₂ muscarinic antagonist, in further combination with an acetylcholinesterase inhibitor and a pharmaceutically acceptable carrier.

12. A kit comprising, in a single package, one container comprising a dual histamine H₃ antagonist/ m₂ muscarinic antagonist in a pharmaceutically acceptable carrier, or separate containers comprising a histamine H₃ antagonist in a pharmaceutically acceptable carrier and a m₂ muscarinic antagonist in a pharmaceutically acceptable carrier, and another container comprising an acetylcholinesterase inhibitor in a pharmaceutically acceptable carrier.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
19 September 2002 (19.09.2002)

PCT

(10) International Publication Number
WO 2002/072093 A3

(51) International Patent Classification⁷: A61K 31/445,
A61P 25/28, A61K 31/4525, A61P 25/00

(21) International Application Number:
PCT/US2002/003975

(22) International Filing Date: 6 February 2002 (06.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/267,352 8 February 2001 (08.02.2001) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

— *with international search report*

(88) Date of publication of the international search report:
22 January 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(71) Applicant: SCHERING CORPORATION [US/US];
2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(72) Inventors: HEY, John, A.; 23 Willow Avenue, Randolph, NJ 07869 (US). ASLANIAN, Robert, G.; 144 Philip Drive, Rockaway, NJ 07866 (US).

(74) Agent: MAGATTI, Anita, W.; Schering Corporation, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(54) Title: USE OF DUAL H₃/M₂ ANTAGONISTS WITH A BIPYRIDINIC STRUCTURE IN THE TREATMENT OF COGNITION DEFICIT DISORDERS

(57) Abstract: This invention relates to the use of a dual histamine H₃ receptor antagonist / m₂ muscarinic antagonist, or a combination of a histamine H₃ receptor antagonist and a m₂ muscarinic antagonist, optionally in further combination with an acetylcholinesterase inhibitor, for the preparation of a medicament for the treatment of cognition deficit disorders.

WO 2002/072093 A3

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 02/03975

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/445 A61P25/28 A61K31/4525 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 05292 A (SCHERING CORP) 12 February 1998 (1998-02-12) cited in the application	1-3,6, 9-12
Y	abstract; examples 53,467-469 page 8, line 10 -page 9, line 14 ---	1,3,4,6, 7,9-12
X	BOYLE C D ET AL: "Benzylidene ketal derivatives as M2 muscarinic receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 24, 18 December 2000 (2000-12-18), pages 2727-2730, XP004225337 ISSN: 0960-894X	1-3,6, 9-12
Y	abstract; table 2 --- -/--	1,3,4,6, 7,9-12



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the International filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the International search

3 October 2003

Date of mailing of the International search report

21/10/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

A. Jakobs

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/03975

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>YATES STEPHEN L ET AL: "Identification and pharmacological characterization of a series of new 1H-4-substituted-imidazol histamine H3 receptor ligands."</p> <p>JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,</p> <p>vol. 289, no. 2, May 1999 (1999-05), pages 1151-1159, XP002256538</p> <p>ISSN: 0022-3565</p> <p>the whole document</p> <p>---</p>	1,3,4,6, 7,9-12
Y	<p>LIGNEAU X ET AL: "Neurochemical and behavioral effects of ciproxifan, a potent histamine H3-receptor antagonist"</p> <p>JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US,</p> <p>vol. 287, no. 2, November 1998 (1998-11), pages 658-666, XP002239628</p> <p>ISSN: 0022-3565</p> <p>the whole document</p> <p>---</p>	1,3,4,6, 7,9-12
Y	<p>LEURS ROB ET AL: "Therapeutic potential of histamine H3 receptor agonists and antagonists."</p> <p>TRENDS IN PHARMACOLOGICAL SCIENCES,</p> <p>vol. 19, no. 5, May 1998 (1998-05), pages 177-183, XP004121095</p> <p>ISSN: 0165-6147</p> <p>page 180, column 1, paragraph 5 -page 181, column 1, paragraph 2; figures 1-3</p> <p>page 182, column 2, paragraph 3 -page 183, column 1, paragraph 2</p> <p>---</p>	1,3,4,6, 7,9-12
Y	<p>US 5 990 147 A (ASLANIAN ROBERT G)</p> <p>23 November 1999 (1999-11-23)</p> <p>the whole document</p> <p>---</p>	1,3,4,6, 7,9-12
Y	<p>MARIA GRAZIA GIOVANNINI ET AL: "EFFECTS OF HISTAMINE H3 RECEPTOR AGONISTS AND ANTAGONISTS ON COGNITIVE PERFORMANCE AND SCOPOLAMINE-INDUCED AMNESIA"</p> <p>BEHAVIOURAL BRAIN RESEARCH, ELSEVIER, AMSTERDAM, NL,</p> <p>vol. 104, no. 1/2, October 1999 (1999-10), pages 147-155, XP001164228</p> <p>ISSN: 0166-4328</p> <p>the whole document</p> <p>---</p>	1,3,4,6, 7,9-12

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/03975

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>ONODERA KENJI ET AL: "The roles of histamine H3 receptors in the behavioral disorders and neuropsychopharmacological aspects of its ligands in the brain." FOLIA PHARMACOLOGICA JAPONICA, vol. 114, no. 2, August 1999 (1999-08), pages 89-106, XP008021117 ISSN: 0015-5691 abstract</p>	1,3,4,6, 7,9-12
Y	<p>MCGURK S R: "THE EFFECTS OF CLOZAPINE ON COGNITIVE FUNCTIONING IN SCHIZOPHRENIA" JOURNAL OF CLINICAL PSYCHIATRY, XX, XX, vol. 60, no. SUPPL 12, 1999, pages 24-29, XP008021126 ISSN: 0160-6689 abstract</p>	1,3,4,6, 7,9-12
Y	<p>NACASCH N ET AL: "CLOZAPINE FOR THE TREATMENT OF AGITATED-DEPRESSED PATIENTS WITH COGNITIVE IMPAIRMENT: A REPORT OF THREE CASES" CLINICAL NEUROPHARMACOLOGY, RAVEN PRESS, NEW YORK, NY, US, vol. 21, no. 2, March 1998 (1998-03), pages 132-134, XP008021125 ISSN: 0362-5664 abstract page 133, column 2, paragraph 2</p>	1,3,4,6, 7,9-12
X	<p>US 2 624 734 A (MISCHA JAMPOLSKY LESTER ET AL) 6 January 1953 (1953-01-06) column 1, line 41-48; example 2</p>	6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/03975

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,3,6,7,9-12 relate to a compound/composition/method/use defined by reference to the following parameters:

P1: H3 receptor antagonist.

P2: m2 muscarinic antagonist.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

Furthermore, according to Rule 6.2.a. PCT, claims shall not, except where absolutely necessary, rely on references to the description. Therefore, the part "and those of formula VIII or IX, and the m2 muscarinic antagonist selected from the compounds of the formula IA-1" in claims 4,5,7,8 has been disregarded.

The compound name "mifetidine" was considered to be an obvious error and read as "mifentidine" in correction.

The expression "cognition deficit disorders" was considered unclear. The lack of clarity is such as to render a meaningful complete search over the whole scope claimed impossible.

Consequently, the search has been restricted to the individual compounds of claim 2,5 and 8 either alone or in combination with a compound selected from the group consisting of thioperamide, impromidine, burimamide, clobenpropit, impentamine, mifentidine, S-sopromidine, R-sopromidine, ciproxifam, SKF-91486, GR175737, GT-2016, GT-2331, UCL-1199, clozapine in relation to the treatment of cognition deficit disorders selected from the group consisting of Alzheimers disease and attention-deficit disorder.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/03975

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9805292	A	12-02-1998	US 5889006 A	30-03-1999
			AT 233260 T	15-03-2003
			AU 724001 B2	07-09-2000
			AU 3899997 A	25-02-1998
			BR 9711119 A	23-11-1999
			CN 1232462 A , B	20-10-1999
			CZ 9900366 A3	16-06-1999
			DE 69719354 D1	03-04-2003
			EP 0938483 A2	01-09-1999
			HU 9902827 A2	28-08-2000
			JP 2000501117 T	02-02-2000
			KR 2000029947 A	25-05-2000
			NO 990551 A	07-04-1999
			NZ 333801 A	28-04-2000
			PL 331534 A1	19-07-1999
			SK 15599 A3	13-03-2000
			TR 9900255 T2	21-07-1999
			WO 9805292 A2	12-02-1998
			US 6043255 A	28-03-2000
			ZA 9707011 A	06-02-1998
<hr/>				
US 5990147	A	23-11-1999	NONE	
<hr/>				
US 2624734	A	06-01-1953	NONE	
<hr/>				